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The purpose of this project was to understand rapidly-induced and persistent forms of synaptic memory. The properties of the synaptic modifications underlying this plasticity could account for some of the adaptive and self-organizing capabilities of simple and well-defined neurobiological networks in the mammalian brain. These can be studied rigorously using neurophysiolog cal and optical techniques. Spearheading the project effort was the working hypothesis that long-term synaptic potentiation (LTP), a use-dependent enhancement of synaptic transmisssion, may mediate certain mnemonic functions of hippocampal circuitry and other forebrain structures. The project was organized around four categories of interrelated specific aims. First, new quantal analysis methods were developed and tested (Aim 2) using patch-clamp techniques to stu charge fluctuations of synaptic transmission during LTP at the crayfish neuromuscular junction Accomplishment of this aim was necessary in order to be able to transfer and apply the new met to analyze and learn the biophysical mechanisms underlying LTP in hippocampal synapses (Aim 1) a much more difficult preparation to study at this level. Third, development and utilization

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19. ABSTRACT (Continued from front page)

of hippocampal cultured slices to study the role of individual neurons and synapses during LTP (Aim 3) may prove particularly advantageous because both quantal analysis and other powerful approaches can be applied to understand the cellular neurobiology of hippocampal synapses and circuitry. Fourth, development and application of optical techniques for use in both acute ar cultured hippocampal slices has provided a means to determine whether structural changes accon pany activity-dependent biophysical modifications of synaptic function (Aim 4). These results have been summarized and integrated into a framework that has posed theoretical questions about synaptic modification rules for neuroplasticity in a way that can be tested both by computer simulations and experimentally in acute and cultured brain slices.

I. OBJECTIVES OF THE RESEARCH EFFORT

A. **General.** To understand the molecular and biophysical mechanisms of learning and memory in neurophysiological terms remains a prize goal of neurobiology. The synaptic learning hypothesis postulates that long-term synaptic potentiation (LTP) might mediate some of the mnemonic functions of the hippocampus and other structures in the mammalian central nervous system. LTP is a leading candidate mechanism whereby information could be stored at the synaptic level and possibly give rise to the associative, encoding, and retrieval capabilities of neuronal networks.

Recent support for this hypothesis has come from the discovery of a Hebb-like conjunctive mechanism that mediates the induction of associative LTP in a particular subset of synapses in the hippocampus (Kelso et al, 1986). While the main goal of this project has remained to understand the biophysical and molecular mechanisms that underlie the induction, maintenance, and expression of LTP, a major thrust of the effort within the last year was to summarize and integrate these AFOSR-supported breakthroughs into a more general theoretical and experimental framework (Brown et al, 1988,1989, 1990). The result has been the elucidation of several modification rules or algorithms for synaptic modifications that may underlie learning and perceptual organization (Brown et al,1989, 1990). These rules can be rigorously tested experimentally and by computer simulation.

B. **Specific.** Earlier advances toward understanding the molecular and biophysical mechanisms of LTP have served an important foundation upon which to build the specific aims of this project. The successful application of single-electrode voltage clamp (SEC) to hippocampal synapses (Brown and Johnston, 1983) and the study of LTP at hippocampal synapses using this new technology (Barrionuevo et al, 1986; Griffith et al, 1986; Kelso et al, 1986) led to the realization that in order to determine the proximal cause for the synaptic modification during LTP, a meaningful quantal analysis of the process was required. The viability of the major hypotheses for LTP depend on the outcome of these experiments! The specific aims below were designed to allow a multipronged but highly interrelated approach to achieve this end.

1. *Quantal analysis.* To accomplish this phase, the development and implementation of new mathematical methods to perform a quantal analysis were required in order to circumvent certain theoretical problems inherent in the more "classical" methods (see Aim 2 below). Study of the charge fluctuations *under voltage-clamp conditions* during LTP is necessary to perform the analysis. Achievement of the second aim of the project was needed to provide the vehicle for the first to be accomplished.

2. *Develop patch-clamp technology and algorithms for fluctuation analysis.* The most suitable solution to create a new method of quantal analysis was to apply the patch-clamp method to the crayfish neuromuscular junction where the optimum method could be selected and tested under ideal conditions. The reason this combination was chosen was that the three classical methods of quantal analysis had already been applied to the study of LTP at this crayfish synapse (Baxter et al, 1985), so the new method could be directly compared against what was known about the LTP-associated changes in quantal release parameters of this synaptic system.

3. *Develop and utilize the cultured hippocampal slice preparation for studies of the role of individual neurons and synapses in LTP.* The development of cultured hippocampal slices was highly desirable because accessibility to specific neurons and synapses visually and electrophysiologically is easy compared to that in acute slices. Equally important was the observation that neural interconnectivity is fairly well retained in a topographical configuration that is easily recognized as "hippocampal". This provides the advantage that the contributions of individual cells and synapses during LTP to a network-like matrix of cells and connections (that is similar to the "natural" interconnected matrix in the brain) can be evaluated using SEC and patch-clamp techniques in combination with optical techniques during quantal analysis (Aim 1) and structure /function studies (Aim 4) of synaptic plasticity.

4. *Determine whether activity-dependent movement accompanies synaptic modifications during plasticity.* Recent evidence strongly supports the notion that even in the adult, in addition to functional plasticity, there are dynamical structural changes. Whether such changes result from or directly contribute to activity-dependent functional changes such as LTP and learning is not known. The development of new imaging techniques, excellent optics, and new fluorescent probes now permits optimal use of these techniques and optics (video-enhanced, differential interference contrast and fluorescence microscopy, and more recently, confocal scanning laser microscopy). Improved resolution, real-time image acquisition, and computer-assisted measurement techniques provide the means to directly test the idea that synapses move or change in shape or size to contribute directly to functional synaptic modifications.

II. STATUS OF THE RESEARCH EFFORT

A. **General.** Significant progress has been made toward attainment of each of the specific goals of this project! This headway has been propelled in part by the insights gained from the approach used which, as stated above, has been to combine sound experimental design with theoretical considerations and computer simulations. The inroads made during the last year, which are reviewed

later, were substantial considering the major disruption to the research effort brought about by the move from the west coast to the east coast. Fortunately, through a coordinated move of lab personnel and equipment, experimental downtime was minimized. During the move, continued computer simulations and writing made it possible to complete several manuscripts (discussed below).

The lab is now up and fully operational. The key scientists and lab assistant -- Keenan, Kairiss, Chapman, and Stevens-- relocated with me. In addition I have five new graduate students, who will contribute heavily to the research effort as, well as five undergraduates who are surprisingly good at the computer simulations.

In this period a series of manuscripts were completed that summarized and integrated molecular, biophysical, and computational aspects of LTP Brown et al, 1988, 1989,1990). It was shown how experimental details about the function of the N-methyl-D-aspartate receptor/ionophore complex at the biophysical and molecular levels contributed to understanding the role of these molecules as an AND-gate in the induction of associative LTP. Theoretical work based on compartmental simulations of conductance changes in dendrites and their spines was shown to be essential for understanding the role of these neuronal compartments in the induction and expression of LTP. More generally, it was pointed out that formalizing, simulating, and testing various models of LTP (at the molecular level, the cellular or compartment level, or at the network level), if based on available and sound experimental data, can be extremely valuable as a validation tool for differentiable hypotheses. We emphasized the power of combining rigorous experimental study and theoretical approaches for clearly understanding and then solving problems in neurobiology. This synthesis has resulted in a more precise formulation of three hypotheses for induction and three hypotheses for the expression of LTP that can be tested and differentiated experimentally. It also began to forge linkages between experimental neurobiology and computational neuroscience.

On the experimental front, several features of hippocampal LTP learned from experimentation in this and other labs over the course of the last year have served to provide a clearer framework in which to study it and think about it. As we have suggested elsewhere, it is conceptually useful to consider the problem of understanding LTP at three different levels: induction, maintenance, and expression. "Induction" is the initial sequence of events that puts the modification process into motion. "Expression" refers to the set of mechanisms that constitute the proximal cause of the synaptic enhancement. "Maintenance" pertains to the factors that govern the duration of the enhancement and couple the triggering events to the expression (Brown et al, 1988, 1989) The mechanism for induction is different at the Schaffer-collateral/commisural synapses in CA1 from that at the mossy-fiber synapses in CA3. From this information we infer that mechanisms responsible for maintenance and expression may also be different at different synapses.

Recent work indicates that at least two kinds of LTP occur in the hippocampus, each kind possibly mediated by separate biochemical and molecular events (Brown et al, 1989). Whether

associative LTP, which is dependent on Hebbian mechanisms in CA1 synapses, occurs at other hippocampal synapses remains to be discovered. Consideration of these distinctions underscores the amount of work still required to determine the similarities and differences in mechanisms at different synapses of the hippocampus that lead to a common endpoint --that LTP induced by previous synaptic activity results from an increase in the measured synaptic conductance produced by the monosynaptic excitatory input. The specific aims of this project are pertinent to understanding LTP in the context that it is not a simple, nor single process. Achievement of the aims have begun to help us toward unraveling the biophysical and molecular events underlying each of the three aspects of LTP at the different synapses of the hippocampus

B. Specific.

1. *Quantal analysis experiments to determine the mechanism underlying LTP.* The application of single-electrode voltage clamp (SEC) to study hippocampal synapses during LTP (Barrionuevo et al, 1986; Griffith et al, 1986; Kelso et al, 1986a,b) was a major technological accomplishment that ushered in an era where quantal analysis of the mechanism for LTP could be achieved realistically. For such an endeavor new analytical methods had to be developed. Our voltage-clamp recordings of spontaneous miniature synaptic currents (Rong et al, 1987; Keenan and Brown, unpublished) in CA3 neurons suggests that the mean quantal size is no larger than 1 nS. Other previously used models have made unrealistic assumptions about the quantal size density distributions as well as the nature of the probability release function (previously assumed in error to be Poisson). Our solution was to develop a maximum-likelihood approach (see below) to enable us to begin a quantal analysis of LTP that relied on no inappropriate or unrealistic assumptions. This requirement satisfied now makes possible the attainment of Aim 1.

2. *Develop patch-clamp technology and algorithms for fluctuation analysis.* A maximum-likelihood method for estimating quantal parameters before and after LTP induction has been completed in collaboration with Elliot Landaw at UCLA. The main features of the method are that (1) the quantal size density distribution can be Gaussian or Gamma distributed, (2) it allows for quantal variance, (3) the probability release function can be Poisson, binomial, or compound binomial, and (4) it assumes a Gaussian noise term which can be assessed directly from the data. The typical model has six parameters, two of which (the mean and variance of the noise) are assessed from the data. Only two of the remaining four parameters need to be relied upon for the present analysis (m, the mean quantal content, and q, the mean quantal size). Furthermore, this method furnishes standard

errors for all the parameter estimates, extremely important in evaluating confidence levels for changes in quantal parameters during LTP.

Crayfish data (obtained using loose patch-clamp techniques from the crayfish neuromuscular junction before and during LTP (Keenan and Brown, 1986; Keenan et al, 1987) were successfully tested using this method on a mainframe computer at UCLA. The program was then installed on both an IBM AT and a Macintosh II. Although debugging the program on these machines has been a lengthy undertaking, progress has been encouraging with the net result that only one subroutine remains to be fixed. Other fluctuation data obtained from hippocampal CA3 neurons under voltage-clamp conditions (Rong et al, 1987) will also be tested once we are confident of the reliability, accuracy, and precision of the method for extracting the quantal parameters based on the testing of the crayfish data.

3. *Cultured slices and microscopy.* We have successfully cultured slices of both hippocampus and amygdala (Ganong et al, 1988; Stevens et al, 1988). Although the major developments were achieved in California, we have already been able to produce cultured slices here at Yale. The hippocampal cultures have survived more than four weeks with flattening of the pyramidal and granule cells into monolayers. These are criteria used by Dr. Gahwiler, who developed the method at the Max Plank Institute in Germany, as indicators of successful culture. Furthermore, intracellular recordings from pyramidal cells have provided evidence for the viability of the cells and normal electrophysiological properties. These properties include normal input resistances, resting membrane potentials, and normal spontaneous and evoked synaptic responses. Both excitatory and inhibitory synaptic potentials were observed. More importantly, LTP has been induced by synaptic stimulation in these cells. Intracellular dye injections into hippocampal neurons revealed that qualitatively the morphology of the neurons are similar to that in acute slices from young adults.

Neurons of both hippocampal and amygdala cultured slices have been imaged using video-enhanced contrast, differential interference contrast (VEC-DIC) microscopy (Brown and Keenan, 1987; Ganong et al 1988; Keenan et al 1988; Stevens et al, 1988). Information about morphology obtained by fluorescence microscopy is supplemented by the fact that we are able to visualize cellular and subcellular structures in great detail and with extremely good resolution. This method makes application of patch-clamp techniques to quantal analysis of LTP a realistic approach at identifiable synapses of vertebrate central neurons. Furthermore, the ability to see clearly probable sites of cellular contact and interaction, such as synaptic profiles, improves the possibility of being able to record simultaneously (1) biophysical and (2) activity-dependent structural changes, if they occur. The preparation is optimally suited to use of both loose-patch and whole cell or GigaOhm seal patch recording because the ability to visualize the positioning of the electrode onto sites of probable synaptic

contact will enable us to determine biophysical contributions of pre- and/or postsynaptic events to the neuroplasticity of LTP.

One important consequence of having monolayers of interconnected neurons in cultured hippocampal slices is that the general "wiring" of the hippocampal formation is preserved. Mossy fiber inputs to CA3 neurons from granule cells and Schaffer collateral synapses from CA3 to CA1 neurons are retained. This preservation of synaptic contacts should enable us to begin evaluating the contributions of individual neurons and synapses in a matrix to the changes in network output function during LTP that may relate directly to the mnemonic functions of the hippocampus.

Realistic synaptic modification rules that describe how neuronal circuitry of the hippocampus participates in learning and memory functions will require additional knowledge. In addition to what we understand of LTP mechanisms at the biophysical and cellular levels, we will need to learn how plasticity at synapses of individual neurons contributes to transform network or matrix function during LTP and other forms of neuroplasticity. The cultured slices provide a means to test ideas about these transform mechanisms. By using a battery of experimental approaches in combination with computer simulations of networks (modeled after hippocampal circuitry) that have the synaptic modification rules incorporated into the network connections, we can hope to explore the range of adaptive capabilities of these realistically represented networks and compare the results with the neurobiological systems. Bridging the gap between well-characterized neurobiological principles of adaptive change and the emergence of more cognitive functions may provide the insight about the relevance of LTP to the control of adaptive behavior.

4. *Synaptic visualization to determine whether activity-dependent movement accompanies synaptic modifications during plasticity.* Evidence is accumulating that structural changes in adult central synapses are not rare and may be exceedingly dynamic. We wished to test the idea that specific synapses in the hippocampus could be visualized sufficiently well in living slices to permit detection of movement or structural change. In acute living hippocampal and amygdala thin slices we evaluated the resolution and capabilities of VEC-DIC microscopy to study cellular and subcellular structures. Correlative data implied that mossy-fiber expansions (which by classical Golgi and other histological techniques are known to be the synapses of granule cells of the dentate gyrus onto CA3 pyramidal cells) could be visualized (Brown and Keenan, 1987; Keenan et al, 1988). The size, spatial distribution, and developmental time of appearance of these structures corresponded to that described by Amaral and Dent (1981) for the mossy-fiber synapses of the rat, although we have not verified directly that the structures are identical

Direct verification that the profiles we studied are indeed living mossy-fiber terminals has proven difficult. Attempts to match presumptive mossy-fiber expansions with the fluorescing structures has after filling granule cells have provided only a few instances where the match was good

enough to be certain. One problem is that the terminals bleach so rapidly when illuminated at high magnification that there is insufficient time to resolve identity. Another possibility is that the excitation wavelength of light is photolytically damaging the profiles as soon as they are illuminated at high magnification. Low intensity illumination and the capability to record low intensity fluorescence would circumvent this problem, but the solution would require the purchase of a SIT camera with the capability to image at low light intensities in combination with our existing VEC-DIC system.

We have attempted to resolve the problem by developing two other methods to look at mossy fiber terminals using combined fluorescence and VEC-DIC techniques. Both involve the use of vital stains that appear to stain specifically presynaptic terminals. The carbocyanine dye, DODCI, used by Dan Johnston's lab too stain and localize dissociated mossy-fiber terminals for patch recording calcium currents (Gray and Johnston, 1988) was bath applied for ten minutes to acute hippocampal slices that were subsequently viewed using fluorescence and VEC-DIC microscopy. The mossy-fiber terminal field in the dentate gyrus (where collaterals of granule cell axons form varicosities) and in the stratum lucidum of CA3 (where the large mossy fiber expansions can be found) were prominently labeled with the dye. At higher magnification, the brightness of the fluorescence could be attributed to the large size of the bodies that had taken up the dye compared to fluorescence from much smaller structures (< 1.0 μm^2) in other areas of the hippocampal formation. From preliminary measurements taken from adult rat hippocampal slices, the larger fluorescing profiles appear to be in the size range characteristic for mossy fiber collateral varicosities and expansions (7.5 - 16.6 μm^2; Dent and Amaral, 1981).

The other method utilized a zinc chelating fluorescent probe (toluene sulfonamide quinoline, TSQ) which stains only the pool of zinc that is sequestered in the boutons of axons (Frederickson et al, 1987). The high level of zinc in the mossy fiber terminals is well-known and gives rise to the delineation of that synaptic system by the Tim's staining method. As in the other method, we were able to visualize the fluorescence that was highly localized to the dentate gyrus and the mossy-fiber terminal field in CA3 stratum lucidum. We are pursuing these encouraging results with experiments to determine whether the profiles we reported are mossy-fiber terminals.

Since arriving at Yale, we have set up and are currently imaging neurons and dendritic spines of hippocampal and amygdala slices using the confocal scanning laser microscope. The capabilities of this system to study structure-function relationships in neuroplasticity are just now beginning to be tested. Already the results are impressive.

VEC-DIC and confocal scanning laser microscopy are but two manifestations of the driving force of technology which is carrying the study of neuronal structure-function relationships from within prescribed systems based on fixed tissue into new and uncharted areas based on the dynamics of living tissue. New discoveries will possibly force us to revise major concepts about the role of structural elements in neuroplasticity that occurs on a second to second timescale but which has the potential for modifying and controlling the neuronal circuitry that gives rise to adaptive behavior.

III. PUBLICATIONS

A. In Print (1986-1988)

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B. **In Press**

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Keenan, C.L., Baxter, D. and Brown, T.H. Multiplicative interaction between synaptic facilitation and long-term potentiation. J. Neurophysiol.

IV. PROFESSIONAL PERSONNEL

A. **Visiting Scientists.** Patricia Rinaldi, (Division of Neurosurgery, University of California at Irvine); Xin-Wei Rong (Shanghai Institute of Physiology, China).

B. **Associate Research Scientists.** Claude L. Keenan*; Edward. W. Kairiss*

C. **Postdoctoral fellows.** Paul F. Chapman*; Alan H. Ganong (presently at Pfizer, CT); German Barrionuevo (presently at Department of Psychobiology, University of Pittsburg, PA); Steven R. Kelso (presently at Department of Biological Science, University of Illinois, Chicago, IL).

D. **Graduate Students.** Anders Greenwood *(Ph.D. student, Department of Physiology); Anna Nobre* (Ph.D. student, Department of Psychology); Laura Rihm* (Ph.D.

student, Department of Neuroanatomy); Xi-Xiu Xiang* (Ph.D. student, Department of Psychology,); Tony Zador* (M.D., Ph.D. student, Neuroscience); Joanne Goh (University of Bristish Columbia, Ph.D. student in Pharmacology; laboratory of B.R. Sastry)

E. **Undergraduate Students.** Zach Mainen *(Psychology); David Shineburg* (Computer Science); Laura Meyer* (Psychology); Robert Riker* (Computer Science); Victoria Chang (Princeton University); Barbara Chang (CalTech).

*At Yale University

V. INTERACTIONS

A. Presentations

1. Seminars (since 01/86)

02/18/89	"Hebbian synapses and the memory system" Yale Neuroscience Retreat, MBL, Woods Hole, MA.
04/06/88	"Hippocampal LTP in two synaptic systems", Stanford University, Stanford, CA.
03/16/88	"Hippocampal LTP in two synaptic systems", University of California, San Diego, CA.
11/3087	"Associative LTP", Air Force Review, Brook AFB, San Antonio, TX.
11/05/87	"Two biophysical mechanisms for hippocampal LTP", Mill Hill, London, England.
05/22/87	"Hebbian synapses", University of Southern California, Los Angeles, CA.
05/15/87:	"Biophysical and molecular mechanisms of long-term potentiation in hippocampus", Neuropsychiatric Institute, University of California, Los Angeles, CA.
04/22/87:	"Pseudo-Hebbian synapses and glutamate receptors", Beckman Research Institute of the City of Hope, Duarte, CA.
04/10/87:	"Pseudo-Hebbian synapses and glutamate receptors", Brandeis University, Waltham, MA.
04/08/87:	"Long-term synaptic potentiation in the hippocampus", Yale University, New Haven, CT.

03/13/87: "Pseudo-Hebbian synapses and glutamate receptors", University of California, Irvine, CA.

01/20/87: "Pseudo-Hebbian synapses and glutamate receptors",Helmholtz Group Meeting, University of California, Irvine, CA.

01/06/87: "Hebbian synapses in hippocampal circuits", Department of Neurobiology, NIH, Bethesda, MD.

12/17/86: "Hebbian synapses in hippocampal circuits", California Institute of Technology, Pasadena, CA.

12/01/86: "Hebbian synapses in hippocampal circuits", Yale University School of Medicine, New Haven, CT.

10/07/86: "Cellular analysis of long-term potentiation", University of Tennessee, Memphis, TN.

02/19/86: "Neurophysiology of long-term potentiation", Univesity of Southern California, Los Angeles, CA.

01/23/86: "Synaptic substrate for learning", University of Southern California School of Medicine, Los Angeles, CA.

2. Symposia and Workshops (since 01/86)

1988: Workshop--"Hippocampal synaptic plasticity and its modulation" (1st Spring Hippocampal Research Conference, St . Thomas, U.S. Virgin Islands).

1987: Workshop--"Central synaptic transmission" (Second World Congress of Neuroscience, Budapest, Hungary)

Symposium--"Neural plasticity" (1987 Gordon Research Conferences, Wolfeboro, NH)

Symposium--"Competition and cooperation in neural nets" (U.S.-Japan Seminar, University of Southern California, LosAngeles, CA)

Symposium--""Neural models of plasticity: theoretical and empirical approaches" (Marine Biological Laboratory, Woods Hole, MA)

Workshop--"Long-term potentiation: from organism to molecule" (11th Annual Conference on Learning and Memory, Park City, Utah)

1986: Symposium--"Cellular substrates for learning: vertebrate and invertebrate" (16th Annual Society for Neuroscience Meeting Symposium, Washington, D.C.)

Symposium--"Experimental Analysis of simple neuronal networks" (2nd Annual Symposium on Networks in Brain and Computer Architechture, North Texas State University, Denton, TX)

B. **Consultative** N.A.